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Arthritis, Rheumatic Diseases, and Related Disorders

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

Arthritis is a group of disorders that can affect not only the joints but also other connective tissues of the body. These include important supporting structures such as muscles, tendons, and ligaments, as well as the protective coverings of internal organs. Strictly speaking, the word "arthritis" means joint inflammation, although it is often used more broadly to indicate any joint or connective tissue disorder. These diseases are also frequently referred to as the rheumatic diseases.

As scientific knowledge about the rheumatic diseases has grown, their complexity has become more apparent. Authorities now list more than 150 different disorders under that heading. Each is a distinct disease with different potential causes and different prospects for recovery. Treatment must be tailored for the type of arthritis and for the individual patient.

At present, rheumatic diseases affect more than 37 million Americans--approximately one in seven of our population. Arthritis, the Nation's number one crippler, can afflict people of all ages. Moreover, arthritis is usually chronic and can last a lifetime.

According to a recent study at the Multipurpose Arthritis Center at Harvard Medical School and Brigham and Women's Hospital, Boston, patients with osteoarthritis or rheumatoid arthritis had restricted activity, on the average, for at least 1 week of each month. Among students and working patients, an average of 2.5 work days per month were lost due to arthritis. In addition, 30 percent of patients with arthritis were unemployed or had retired early because of impaired health. According to the Arthritis Foundation, about 26.6 million days are lost from work each year due to this disease.

The Arthritis Foundation has stated that the economic costs of arthritis in terms of lost wages and medical expenses are more than $14 billion per year. Because one-third of those with arthritis are 65 years of age or older, much of this economic burden falls on public resources such as Medicare and Medicaid.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) leads and coordinates the Federal biomedical research efforts against the many

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forms of arthritis. Through its extramural programs of grants and contracts, the Institute supports research projects at universities, medical schools, and other research institutions throughout the country. In addition, NIADDK conducts an intensive intramural research program.

NIADDK RESEARCH HIGHLIGHTS

Although medical science has not yet found a cure for many of the forms of arthritis, significant progress has been made through both basic and clinical investigations. Selected highlights of recent research supported by NIADDK follow.

Osteoarthritis

Degenerative joint disease or osteoarthritis--the most common type of arthritis--afflicts more than 16 million Americans. Osteoarthritis primarily affects the cartilage of the joint, causing it to fray, wear, ulcerate, and in extreme cases, to disappear entirely, leaving a bone-on-bone joint. At the edges of the joint, spurs may form. Disability most often results from disease in the weight-bearing joints (knees, hips, and spine).

Investigators are using a variety of approaches to better understand why and how osteoarthritis occurs and to improve therapy for the disease.

Dr. Van Mow, a grantee at Rensselaer Polytechnic Institute, Troy, New York, has developed an apparatus to measure the micromechanical quality of normal and arthritic cartilage. Cartilage tissue contains two major organic substances, collagen (the major protein in connective tissue) and proteoglycans (sugar, protein complexes, and water). The ability of cartilage to take the shocks and loading in joints during daily activity is related to how the collagen, protein, and water move inside the tissue. Osteoarthritis may be a consequence of wear and tear of articular (joint) cartilage. This new technique, which measures the properties of cartilage and its components, may allow researchers to explain the role of mechanical factors in the development of arthritis.

In a study that may someday benefit patients with osteoarthritis, NIADDK grantee Dr. David Howell and associates at the University of Miami School of Medicine demonstrated that they were able to improve the damaged cartilage of a rabbit with osteoarthritis by using weekly injections of a drug known as arteparon. Arteparon appears to work by inhibiting the action of enzymes that are responsible for the destruction of cartilage.

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Rheumatoid Arthritis

This disease affects more than 7 million Americans and is the major crippling disorder among the chronic rheumatic diseases. Rheumatoid arthritis, a chronic inflammatory disease of unknown cause, affects twice as many women as men. The primary target of rheumatoid arthritis is the synovium (joint lining). This tissue, which normally should be smooth and shiny, becomes inflamed, painful, and swollen. Rheumatoid arthritis is also a systemic disease and can cause such general symptoms as weakness, fatigue, and loss of appetite. The disease tends to be both chronic and irregular--it waxes and wanes, and is frequently disabling.

Viruses may be a factor in causing rheumatoid arthritis. Grantee Dr. Carol A. Smith at the Montefiore Medical Center in New York and her associates have identified a small virus, a parvovirus, present in the joint tissues of people with rheumatoid arthritis. The virus, designated RA-1, has shown similarities to parvoviruses, which have been linked to certain diseases in dogs, cats, and mice. Using antibodies against the virus, the scientists found that 13 of 14 joint tissue samples from rheumatoid arthritis patients had evidence of the virus. When they tested the antibodies in the control group of eight patients with osteoarthritis, a different form of arthritis, the scientists found no traces of the RA-1 virus.

Research continues on more effective therapies for rheumatoid arthritis, including the use of retinoids, drugs used for a variety of skin disorders. NIADDK intramural scientist Dr. Ronald Wilder has demonstrated that oral doses of 4-hydroxyphenyl retinamides markedly reduced chronic synovitis (inflammation) in rats with "bacterial cell wall arthritis," an experimentally induced arthritis that resembles human rheumatoid arthritis.

Relatively few drugs are effective for treating severe rheumatoid arthritis. However, an anticancer agent, methotrexate, has been found to be effective against psoriasis and psoriatic arthritis, with relatively minor side effects. Results of a comprehensive multicentered clinical trial supported by an NIADDK contract and led by Dr. John Ward, University of Utah, director of the Coordinating Center for the Cooperative Systematic Studies of the Rheumatic Diseases, indicate that low doses of methotrexate may be very effective therapy for patients with severe rheumatoid arthritis not responding to other forms of treatment. In a double-blind study comparing the effects of methotrexate and a placebo, the researchers reported a reduction of pain and swelling in more than 50 percent of rheumatoid arthritis patients on methotrexate.

Destruction of the diseased joint lining (synovium) by injection of radioisotopes may be an alternative to surgery

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for patients with severe rheumatoid arthritis of the knee. Using this method, NIADDK grantee Dr. Clement B. Sledge at the Brigham and Women's Hospital in Boston found an 80 percent rate of improvement in symptoms for up to a year in 53 patients with severe rheumatoid arthritis of the knee that had not improved with drug therapy.

Systemic Lupus Erythematosus

Lupus, a potentially serious, complicated, inflammatory connective tissue disease, can affect many parts of the body, including the joints, skin, and internal organs. According to the Lupus Foundation of America, there are more than 500,000 people in the United States with the disease. Almost 90 percent of the victims are women of childbearing age.

One of the most serious complications of lupus is nephritis, or kidney disease. Lupus patients produce abnormal antibodies that react with their own tissues. These autoantibodies may accumulate in the kidneys, resulting in lupus nephritis. Dr. Bevra Hahn, a grantee at Washington University, St. Louis, Missouri, has shown that anti-DNA antibodies (produced by the new monoclonal antibody technique) given in early life to mice with a disease resembling lupus can prevent the emergence of lupus nephritis (kidney disease). When 6-week-old mice were injected with these monoclonal antibodies, all were found to be alive at 7 months of age, in contrast to a 60 percent mortality rate by this age in untreated mice. The researchers are exploring how this increased survival occurs so that these results might be applied to humans.

Another new aspect of lupus has been the discovery that some babies born to mothers with lupus have either congenital heart block, transient skin lesions, or both. NIADDK grantee Dr. David Norris and associates at the University of Colorado in Denver have found that "neonatal lupus syndrome" is related to the passage of maternal autoantibodies across the placenta to the fetus.

Lyme Disease

In Lyme disease, also known as Lyme arthritis, the primary persistent symptom is joint inflammation resembling rheumatoid arthritis. Since it was first identified in 1975 by NIADDK grantee Dr. Alan Steere of Yale University, New Haven, Connecticut, the disease has been found in hundreds of people along the Atlantic Coast and in some Midwestern and Western states. Early Lyme disease can be diagnosed by its characteristic skin manifestations, rapidly changing organ system involvement, and, if necessary, now by serologic testing. In some patients there may be neurologic problems such as meningitis, cranial neuritis, and inflammation of the spinal nerves. Dr. Steere has found that for patients with

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early Lyme disease, tetracycline appears to be more effective than penicillin or erythromycin, while high doses of intravenous penicillin are recommended for neurologic abnormalities.

Juvenile Arthritis

Arthritis is commonly viewed as a condition affecting adults, particularly the elderly. However, as many as 250,000 children in this country have some form of this painful disease. In juvenile arthritis, one complication can be inflammatory eye disease associated with band keratopathy (a gray opacity below the outer surface of the cornea) that may lead to glaucoma and blindness. Dr. Gordon S. Sharp, a grantee at the University of Missouri, has discovered band keratopathy in certain strains of inbred mice with autoimmune disease. This animal model may help researchers understand why eye problems are associated with juvenile arthritis.

Orthopedic Research and Related Diseases

Osteoporosis

Osteoporosis affects 15 to 20 million Americans, most of them older women, and costs the Nation at least $3.8 billion annually. Osteoporosis is characterized by decreased bone mass that makes the bones more susceptible to fracture, especially in the spine, wrist, and hip. According to a recent NIH Consensus Development Conference, current data point to estrogen and calcium deficiencies as major causes of primary osteoporosis. In order to prevent fractures, the consensus panel, chaired by Dr. William A. Peck, a grantee at the Jewish Hospital of St. Louis, Missouri, recommended estrogen replacement in at-risk postmenopausal women; adequate nutrition, including an elemental calcium intake of 1,000 to 1,500 mg a day; and a program of modest weight-bearing exercise such as walking.

Effective programs of prevention and treatment may be facilitated by recent studies suggesting that there may be two distinct types of osteoporosis related to aging. Dr. B. Lawrence Riggs, a grantee at the Mayo Clinic, Rochester, Minnesota, has found striking differences in the type of bone tissue lost by two groups of patients. Type I osteoporosis, characterized by rapid loss of "spongy" bone, leads to a sharp increase in fractures of the wrist and spine and occurs mainly in postmenopausal women who are 51 to 65 years of age. By contrast, type II osteoporosis, characterized by rapid loss of both spongy and "compact" bone, leads to a sharp increase in fractures of the hip and spine and occurs in a large proportion of women and men who are older than 75 years of age.

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Although most victims of osteoporosis are postmenopausal women, the disease may also be found in men in the same age range. Researchers led by Dr. Riggs have discovered that there is an increased risk of osteoporosis in males who smoked cigarettes, drank alcoholic beverages, or had an associated medical disease known to affect calcium or bone metabolism. Most of these factors are potentially remediable or treatable.

Bone Metabolism

Bone is in a dynamic state of resorption and replacement that is normally in balance. A clearer understanding of substances that influence bone metabolism will make possible new methods of treating bone problems caused by injury or disease.

Grantee Dr. David J. Baylink of the Loma Linda University in California recently discovered a coupling factor that may explain the interconnection between the resorption and rebuilding cycles of bone remodeling. His theory is that a stable, moderate-sized protein is released during bone resorption. This factor, termed human skeletal growth factor, induces a dramatic increase of DNA synthesis and growth rate of new bone--that is, rebuilding--when low concentrations of this substance are added to cultures.

Fluoride is essential in the diet and is thought to be required for normal dental and skeletal growth. Excessive amounts usually can cause increases in skeletal mass, making fluoride potentially useful for such disorders as osteoporosis. NIADDK grantees Dr. John R. Farley and Dr. Baylink at Loma Linda University discovered that fluoride acts directly on bone cells. They found that chick bone cells treated with sodium fluoride increased both in number and in activity of alkaline phosphatase, an enzyme that reflects activity of bone cells. These studies also showed an increased growth of embryonic chick bone in organ culture.

Scoliosis

Scoliosis, a lateral curvature of the spine, occurs in about 2 percent of the population and is usually detected in early childhood or adolescence. Early identification of these children is very important, because treatment with back braces or electrical stimulation of spinal muscles can be effective in preventing the curvature. Grantee Dr. Albert B. Schultz at the University of Michigan at Ann Arbor recently discovered that patients with scoliosis have a central nervous system that is incapable of providing small corrective asymmetric muscle support to counteract minor postural imbalances.

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Another factor in scoliosis may be the incorrect processing of inner ear signals (balancing mechanism in the brain). The natural eye tracking mechanism called nystagmus is a measure of balance control. In testing scoliosis patients, grantee Dr. Richard M. Herman of the Catholic Medical Center, Manchester, New Hampshire, found that a decrease in the eye tracking mechanism is predictive of an increased curvature. He also found that, in 30 percent of the patients studied, learning problems correlated highly with the occurrence of scoliosis.

New Developments in Joint Replacement

Prosthetic joint replacement is a common orthopedic procedure with major impact on the lifestyle of patients. Few replacements have been as successful in relieving pain and dysfunction as that of hip joint replacement. Most artificial hip joint replacements utilize a type of cement to bond the implant to the bone; however, physical stress can eventually cause the cement to loosen. This problem may be alleviated by a new process under investigation by Dr. Jorge Galante, a grantee at Rush-Presbyterian-St. Luke's Medical Center, Chicago. Dr. Galante uses a cementless prosthesis made from a titanium alloy that has a porous surface. Once the implant is inserted, the bone begins to heal itself and grows into the pores of the implant, forming a natural bond with the prosthesis.

Other aspects of joint replacement being studied by NIADDK grantees include those of the elbow and knee joints.

Knee joint replacements have evolved from a fixed pin axis device to a semiconstrained arrangement. Although both methods are rotational, the semiconstrained arrangement is less rigorously attached and allows a rolling motion of one surface over the other, similar to the natural motion of the knee. This method makes for a better long-term attachment.

Preliminary data also suggest success with other joints, such as the elbow, using the design concept of partial constraint.

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National Cancer Institute

Rheumatoid arthritis, like some cancers, is associated with a defect in the immune system. Rheumatoid arthritis patients have high levels of antibody to Epstein-Barr virus (EBV) in their blood but have difficulty controlling EBV-infected cells.

EBV is a herpes-type virus that is ubiquitous in humans; everyone eventually becomes infected. Once a person is infected, the infection remains for life, although it may be at a low level or never present in any pathological or symptomatic form. In healthy people the virus is handled by the immune system.

A unique feature of this virus is that it preferentially infects part of the body's own immune system, the B lymphocytes (a type of white blood cell). B cells are responsible for producing immunoglobulins, the proteins that can function as antibodies. When EBV infects B cells, it activates them to grow, divide, and produce immunoglobulins. Uncontrolled, this virus-induced proliferation of B cells can result in a form of lymphoid cancer.

In studying how the body's immune system responds to EBV, NCI's Dr. Michael Blaese and colleagues compared blood samples from three groups: healthy normal donors who had not yet been infected with EBV, healthy normal donors who had been infected and had developed some immunity to EBV, and patients with rheumatoid arthritis. In one test, EBV was added to cells of the immune system and cultured in the laboratory for 14 days to study the mechanisms that the body uses to control this infection. In cells from healthy donors who had not been infected by the virus, EBV caused B cells to grow continuously and produce immunoglobulin for the 14 days. In cells from EBV-immune healthy donors, addition of EBV initially caused the same increase in B-cell growth and immunoglobulin production. However, after 8 to 10 days this response peaked and then rapidly fell, so that by day 14 EBV-induced immunoglobulin production had been reduced by more than 90 percent of what it had been before the addition of EBV. The scientists found that this dramatic fall was due to the action of another kind of lymphocyte, the suppressor T cell. This cell develops during normal immunity to EBV and prevents it from causing uncontrolled B-cell activation. When the scientists added EBV to cultures of lymphocytes from rheumatoid arthritis patients, they did not find the expected fall in immunoglobulin production, indicating that these patients have a defect in suppressor T cell activity.

In another test, the researchers measured the number of cells that were infected with EBV in normal donors and rheumatoid arthritis patients. Because EBV infection

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persists for life, the number of virus-infected B cells in the blood can be used as a measure of the effectiveness of immune suppressor cell activity. In normal volunteers only about one cell in each million B cells was found to be infected with EBV, while in the arthritis patients 10 times as many B cells were infected with EBV.

These studies show that rheumatoid arthritis patients have a significant defect in the ability of their T cells to control their own EBV-infected B cells. How this immune T-cell problem relates to the pathology of rheumatoid arthritis remains to be clarified. The scientists are continuing to investigate how the healthy body handles this virus and what immune mechanisms are missing in the arthritis patients.

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National Heart, Lung, and Blood Institute

Arthritis and other collagen or connective tissue diseases often affect the lungs, heart, and blood vessels; hence, the National Heart, Lung, and Blood Institute (NHLBI) supports or conducts research on these disorders.

Rheumatic fever--a disease that may follow a streptococcal infection--often attacks the joints, but these problems may subside without causing permanent damage. More serious is heart muscle inflammation (rheumatic carditis) that may attend rheumatic fever episodes. Rheumatic carditis may produce potentially lethal heart rhythm disturbances or congestive heart failure during the acute phase of the attack or result in progressive damage to the heart valves, which may eventually require valve repair or replacement.

Early studies of patients who died from rheumatic heart disease indicated the presence of combined aortic and mitral valve disease in 32 percent of the patients. Other studies found multiple valvular involvement in up to 50 percent of children with a history of rheumatic heart disease.

The replacement of impaired heart valves with man-made valves has increased over the years, especially in older patients and, since the early 1960's, involving multiple valves. Presently, 10 to 20 percent of patients who undergo cardiac valve replacement receive combined aortic and mitral valve implants.

Surgical mortality for patients undergoing this procedure has been a matter of some concern. Although the rate has been declining, surgical mortality has remained at about 10 to 15 percent for the past decade.

NHLBI grantee Dr. Larry W. Stephenson and his colleagues at the Hospital of the University of Pennsylvania and the Children's Hospital of the University of Pennsylvania School of Medicine, Philadelphia, have studied a series of patients who were operated on for combined replacement of aortic and mitral valves. In these patients, various methods of preservation of the heart muscle were attempted and heart valves of different types were evaluated.

The three methods of surgical protection included instilling fluid directly into the coronary arteries, and stopping the heart with cold saline solution or with a cold potassium solution. Of the three methods used, the last proved superior in survival of the patients during and immediately following surgery (1.2 percent in-hospital mortality among the patients receiving the cold potassium versus 11.3 percent for those receiving direct coronary perfusion and 16.7 percent for those who received cold

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saline). Long-term followup, however, found similar mortality rates among the three groups of patients. Overall survival was approximately 85 percent at 1 year and 58 percent at 5 years; these are similar to survival rates of patients reported in the late 1960's before such surgical protection methods were used.

In conclusion, the researchers point out the need for additional studies on means to protect the heart muscle during surgery. They found no clear superiority or inferiority of any of the four types of heart valves that were used, and reported that long-term mortality was related to cardiac symptoms or anticoagulant therapy, unchanged from the situation in years past. At what point in the disease process surgery becomes the optimum treatment remains an open question.

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National Institute of Dental Research

The National Institute of Dental Research (NIDR) conducts and supports research related to arthritis because certain major dental problems such as periodontal diseases have factors in common with the inflammatory processes and immune responses involved in joint diseases. Additionally, NIDR pursues investigations of chronic, acute, and inherited disorders of the human skeletal system.

In collaboration with NIADDK scientists, NIDR intramural researcher Dr. Sharon Wahl and her associates have recently been able to classify arthritis patients into subgroups with common immunologic, pathologic, histologic, and therapeutic characteristics. These studies suggest that clinically active rheumatoid arthritis is actually a group of disorders that share common features. These observations provide important insight into potential disease mechanisms and offer a sound basis for therapy.

In related studies, an experimental animal model for polyarthritis has been effective in assessing the contribution of inflammatory cells to arthritis and to tissue destruction. This disease process is initiated by specific bacteria, which then trigger an immune response. Assessment of the effects of various drug regimens on the development and progression of this chronic inflammatory process can be monitored in this experimental disease state. One such anti-inflammatory agent is cyclosporin A, which is commonly used in transplant patients. Dr. Wahl has found that this drug inhibits the development of chronic arthritis and joint destruction in the animal model, suggesting possible application to the treatment of human rheumatoid arthritis.

Arthritis is associated with degenerative changes in the tissues that comprise the joint capsule and joint lining. One important cell type is the chondrocyte (a cartilage cell) which produces collagen. In patients with arthritis chondrocytes exhibit a change in structure and also a reduction in the synthesis of cartilage-specific collagen. Similar effects are produced when vitamin A is added to chondrocytes in culture. NIDR scientist Dr. Walter Horton is studying the effects of vitamin A on the mechanisms of action of the chondrocyte. This research may lead to a better understanding of degeneration in arthritis at the biochemical and molecular levels.

In related studies, NIDR researcher Dr. Yoshi Yamada and his associates are using techniques of molecular biology to investigate the structure of cartilage collagen and proteoglycan (a component involved in the cushioning function of cartilage). They have prepared DNA probes for cartilage-specific collagen. In collaboration with researchers at The

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Johns Hopkins University Hospital in Baltimore, these scientists are examining DNA in patients with inherited cartilage diseases to determine if alterations exist in the patients' gene structure. Such studies could provide early diagnosis through screening.

In various animal models, absence of some of the components of cartilage matrix has been shown to underlie many hereditary diseases involving cartilage abnormalities. NIDR's Dr. Kenneth S. Brown is studying animal models for clues to genetic human joint disorders. His work has yielded much information about tissue function. These animal models for hereditary arthritis bear similarities to several human arthritis syndromes and may provide a basis for analysis of treatment measures and studies of disease mechanisms.

Drs. Vincent Hascall and Srinivasan Chandrasekhar are continuing their intramural studies of the molecular structure and metabolism of proteoglycans and glycoproteins, two important components of the cartilage matrix. These studies have significant bearing on degenerative diseases such as rheumatoid arthritis, in which early stages of the disease process result in degradation and altered synthesis of the matrix components.

NIDR's Dr. Pamela Gehron Robey has established techniques that provide easy isolation and maintenance of human bone cells from surgical or biopsy specimens. Bone-forming cells, called osteoblasts, can now be obtained from any individual regardless of age or disease status. This breakthrough in bone cell biology provides an exciting new tool to investigate the underlying mechanisms of metabolic and heritable bone disease states.

Under the direction of intramural scientist Dr. John Termine, studies are continuing on the major genetic disease of bone, osteogenesis imperfecta, which results in abnormally brittle bones that are subject to fractures. Three new animal models and a number of patients suffering from one or more clinical forms of the disorder are now under study. The scientists have found this disease to have a significant number of variants in which bone-specific proteins are severely depleted in the diseased bone and improperly distributed in bone cell cultures. These findings provide new prospects for determining the underlying causes of at least some forms of this bone disorder.

Work also continues by NIDR's Dr. Larry Fisher on the development of a radioimmunoassay to determine circulating levels of osteonectin in human blood. Osteonectin is a protein thought to be involved in bone mineralization. Such a test will be an excellent diagnostic tool for the evaluation of bone disease.

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NIDR's Dr. Haridara Reddi is continuing to investigate bone inductive proteins that are active components of demineralized bone matrix powder, a new biomaterial being used in surgical implants. This powder is used to treat a number of craniofacial, periodontal, and orthopedic skeletal defects. He is determining the specific functions of the different components within the bone powder to increase knowledge of bone repair and regeneration.

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National Institute of Neurological and
Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is the national focal point for research on the central nervous system and neuromuscular function. NINCDS-supported investigators study joint movement, treatment and rehabilitation of muscle and joint disorders, and immune and autoimmune systems in animals, patients and healthy volunteers.

Intramural scientist Dr. Roscoe O. Brady directs a broad program of research that may prove useful in understanding arthritis. In his branch, Dr. John A. Barranger and his team are studying ways to replace missing enzymes and defective genes as potential approaches to the treatment of Gaucher's disease, a disorder that affects the bones and joints. Studies of both the cell structure and genetic makeup characteristic of Gaucher's disease may lead to new therapies for arthritis and other bone-related disorders.

Another NINCDS intramural research team, headed by Dr. George Constantopoulos, is studying a group of hereditary diseases called mucopolysaccharidoses, or MPS, which are characterized by joint stiffness. The investigators have contributed to the understanding of how the body's chemistry goes awry in MPS. In addition to human studies, the team is now studying a drug-induced rat model of MPS, along with a canine model in which MPS occurs naturally. Dr. Constantopoulos will use these animal models in therapeutic trials in which he will attempt to replace enzymes that are absent in MPS.

NINCDS grantee Dr. Alan R. Reich, University of Washington in Seattle, is studying a form of arthritis that affects the larynx. To develop a clinical picture of this frequently undetected disorder, Dr. Reich uses a three-tiered approach: computers analyze various features of the patient's speech such as pitch and vibration; ultra-high-speed photography tracks the movements of the vocal system; and staff members trained to listen for abnormal voice characteristics such as hoarseness and breathiness evaluate the patients. In addition to advancing our understanding of arthritis, Dr. Reich's findings are expected to yield new insights into the way the vocal system works and provide a foundation for future investigations of the aging larynx.

Dr. Bruce Leipzig, an NINCDS grantee at the University of Arkansas in Little Rock, has developed a method of reimplanting bone that may one day compensate for bone lost during cancer surgery. Dr. Leipzig removed diseased lower jaw bones from adult dogs and destroyed the diseased tissue

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by subjecting it to extremely cold temperatures using a technique called cryosurgery. By destroying only the unhealthy tissue and immediately reimplanting the segments of healthy bone, Dr. Leipzig was able to successfully induce new bone growth. His technique may prove to be applicable to human bone disease.

With NINCDS support, Dr. Andrew G. Engel of the Mayo Foundation in Rochester, Minnesota, is investigating muscle disorders characterized by inflammation--a major feature of arthritis--in humans, rats, and mice. By examining the origins and development of these muscle disorders, Dr. Engel hopes to define the cells involved and clarify the chemical makeup of the destructive mechanisms. Such knowledge may be beneficial in developing new treatments.

At the Oklahoma Medical Research Foundation in Oklahoma City, Dr. Robert A. Good, an NINCDS grantee, is studying how nutrition affects a patient's length of life and immune system. He is focusing on the phenomena of autoimmunity, a process by which the body's immunological defense system attacks its own tissues. Dr. Good is also studying disorders in which the immune system loses the ability to defend the body from infection. These studies of the immune systems of patients and mice may lead to new treatments in diseases such as arthritis and multiple sclerosis, which are suspected of having a possible autoimmune origin.

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National Institute of Allergy and Infectious Diseases

Arthritis-related research conducted and supported by the National Institute of Allergy and Infectious Diseases (NIAID) focuses on normal and abnormal functions of the immune system, factors involved in inflammation, the possible role of infectious agents, and the influence of genetics. Several significant achievements have been described during this past year.

Lyme disease is one of a number of infectious diseases associated with arthritis signs and symptoms such as inflammation and joint pains. Now that studies have confirmed that a tick-borne spirochete isolated by NIAID's Drs. Willy Burgdorfer and Alan Barbour is the cause of Lyme disease, research is continuing on the epidemiology and ecology of the disease.

In the United States, Lyme disease seems to occur in three distinct geographic areas--the Northeast, the Midwest, and the West. The spirochete, known as Borrelia burgdorferi in honor of Dr. Burgdorfer, is carried by the Ixodes dammini tick in the east and midwest. A different Ixodes tick, I. pacificus, has been identified as a vector in California and Oregon. All Ixodes ticks feed on many species of birds and mammals.

Single cases of Lyme disease have been reported in Texas, Arkansas, and Georgia, suggesting that other species of ticks may also be involved in the transmission of the spirochete. If this is so, Lyme disease probably occurs more widely in the United States than previously assumed.

Lupus is a complex autoimmune disease in which a person's own normal tissue is mistakenly perceived by the body as a "nonself" substance, triggering an inappropriate immune response. This immune response involves a complex network of organs and cells, including two major classes of immune cells, B cells and T cells. B cells secrete antibodies, and T cells help regulate antibody production.

Lupus patients have enhanced B-cell activity and an excess of antibody. In order to understand this phenomenon and find ways to correct it, intramural scientist and now Director of NIAID Dr. Anthony Fauci has developed a model for studying how B cells become activated, divide, and mature into antibody-producing cells.

Using this model system, he and his colleagues have successfully identified and isolated the functional subsets of human B cells. They demonstrated that resting B cells can be activated by a number of initial signals. Following activation, the B cells can respond directly to a number of T cell-derived factors that affect growth and differentiation.

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Dr. Fauci studied the effects of corticosteroids and cytotoxic drugs on B-cell function. These powerful drugs are often effective in reducing inflammation in lupus patients, but how they work is not well understood. He demonstrated that corticosteroids deplete the inducer/helper subset of T cells, benefiting the suppressor subset of T cells. As a result, B-cell function is suppressed. The drugs also exert a selective inhibitory effect on early events in the B cell cycle and have less effect on later phases of the cycle.

The cytotoxic drug cyclophosphamide, administered chronically in low doses, has a more pronounced effect on B-cell function than on T-cell function, since B cells are slower to recover from the drug's suppression of cell division.

As part of the normal immune response, antibodies lock antigens into antigen-antibody complexes, also called immune complexes, thereby triggering other mechanisms that remove the complexes from circulation. A characteristic of lupus patients is the presence in blood and tissues of immune complexes that are not properly cleared from the circulation. Eventually they are deposited in the kidneys and other organs where they trigger inflammation and damage tissues.

Several NIAID-supported scientists are trying to understand this phenomenon. Intramural investigator Dr. Michael Frank has found evidence that immune complexes persist because of a defect in the cells responsible for their clearance. These cells have on their surfaces certain recognition units for one end (the Fc portion) of antibody molecules of the immune complex. A defect in the Fc receptor unit in the lupus patient may affect the ability of the cell to recognize immune complexes and to eliminate them.

Infection with group A streptococci, if not properly treated, can lead to serious, long-lasting diseases such as acute glomerulonephritis (kidney disease), rheumatic fever, or rheumatic heart disease. NIAID grantee Dr. John B. Zabriskie and his colleagues at Rockefeller University in New York have been studying streptococcal diseases for many years, trying to determine why some patients develop serious sequelae. They have identified and described a genetic marker found in patients with rheumatic fever. This marker may serve as a recognition or receptor site for antigens of the infecting streptococcal organism. They have now developed two monoclonal antibodies that will identify 95 percent of all patients with rheumatic fever.

The investigators have also studied the circulating immune complexes in rheumatic fever patients. They determined that the complexes contain several different streptococcal antigens that are unique to streptococcal

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strains associated with rheumatic fever. Complexes isolated from patients with kidney disease contain different antigens. These studies should lead to a better understanding of, and treatments for, rheumatic fever and acute glomerulonephritis.

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National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training that provide the foundation for a better understanding of fundamental life processes. This research supplies new knowledge, theories, and concepts for the disease-targeted programs of other NIH Institutes.

One of NIGMS' major programs supports basic research on genetics. This work may have relevance to arthritis since it is a disease in which heredity plays a part, although in most forms of arthritis no clear-cut pattern of inheritance can be discerned. More than one defective gene and usually environmental influences as well may be involved in so-called multifactorial disorders, including arthritis.

The NIGMS is supporting a number of research grants to develop computer programs and statistical methods that will help sort out the relative contributions of genetics and environmental factors in arthritis and other multifactorial disorders. This research will help determine what specific kinds of information are needed about family history and environmental variables in order to predict an individual's likelihood of developing a multifactorial disease. Better prediction may lead to earlier treatment and, in some cases, prevention.

One grantee, Dr. Robert Elston, Louisiana State University Medical Center in New Orleans, is collecting data on multifactorial disorders and analyzing the data using computer programs. If Dr. Elston identifies a gene as a factor in the cause of a multifactorial disorder, researchers in his laboratory will try to determine the gene's location on one of the chromosomes. In other laboratories, molecular biologists will try to isolate and duplicate the gene for detailed study.

The NIGMS also gives grants to support four genetics research centers intended to bring about collaboration between basic and clinical scientists. The goal of these centers is to accelerate scientific progress by encouraging the development of new concepts and by promoting the application of basic research findings to clinical problems. In the center at the University of California, San Diego, Dr. Jarvis E. Seegmiller and his associates are investigating factors affecting the rate of purine synthesis in patients with gouty arthritis. Excessive synthesis of this compound is believed to be responsible for the abnormal amounts of uric acid found in the blood of these patients.

Last year Dr. Seegmiller discovered that zinc is required for the proper functioning of one of the enzymes

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necessary to maintain normal amounts of uric acid. Further studies of the enzyme indicate that its activity declines progressively with age in normal individuals. Clinical studies that may have implications for the control of gout are now being supported by NIADDK to see if supplemental zinc can alter the enzyme's activity. The progress of this research is an example of how basic studies supported by NIGMS lead to new approaches to further our understanding of specific disorders and aid other NIH Institutes in their disease-targeted investigations.

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National Institute of Child Health and Human Development

The National Institute of Child Health and Human Development (NICHD) supports research to determine if there is any relationship between vasectomy and the use of oral contraceptives and the development of arthritis. The Institute also supports and conducts research on collagen and connective tissue diseases and on immunology and autoimmune disorders.

This past year, NICHD released findings from the largest study to date on the effects of vasectomy on health. This study looked at the incidence of 98 diseases among more than 10,000 vasectomized men and among a similar number of non-vasectomized men. No association was found between the incidence of any type of arthritis and vasectomy. Previous studies with animals suggested at least a theoretical basis for the development of autoimmune disease following vasectomy, but this study found no support for that concern. Dr. Frank J. Massey, Jr., from the School of Public Health, University of California at Los Angeles, coordinated this study under contract to NICHD.

The Institute also has been looking at rheumatoid arthritis in relation to the use of oral contraceptives. Rheumatoid arthritis has been reported to occur less frequently among women who have used the pill. The role of sex hormones in the etiology of this disease has been suspected previously because more women than men have this and because it has been observed that pregnancy improves the symptomatology of rheumatoid arthritis. The NICHD is currently reviewing research proposals to examine this relationship more closely.

The NICHD intramural research program conducts studies on a number of metabolic and connective tissue disorders, including heritable disorders of bone and connective tissue. Dr. Michael Zasloff, in preliminary studies on a rare congenital disease, fibrodysplasia ossificans progressiva (a disorder characterized by pain and swelling in the muscles caused by bone deposits and gradual replacement of muscle tissue by bone), found that six of seven children treated with 13-cis-retinoic acid experienced an apparent remission of ectopic bone formation.

In basic research studies, NICHD-supported scientists are gradually unraveling the complexities of cell differentiation and proliferation for developing cartilage. One group of NICHD-supported scientists, headed by Dr. William B. Upholt at the University of Chicago, is investigating the regulatory mechanisms of different collagen molecules involved in the formation and proliferation of cartilage cells. The information obtained from such studies is

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important because malfunctions of the genes and their protein products that are involved in cartilage formation could have far-reaching ramifications for the treatment of disorders such as arthritis.

Another group of NICHD-supported scientists, headed by Dr. Harvey Colten at Boston Children's Hospital, is studying the complement system. Defects in this system, which is comprised of 20 specific serum proteins that are activated by antigen-antibody reactions, result in increased susceptibility to autoimmune disease or to infections by certain bacteria. Deficiencies of certain components of the complement system have been identified that result in certain clinical diseases. Further research may find a relationship between defects in this system and certain types of arthritis.

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Renal toxicity and gouty arthritis (saturnine gout) are two of the diverse symptoms of lead poisoning. Dr. Walter Farkas, University of Tennessee in Knoxville, is studying the effect of lead on the enzymes of purine (a constituent of DNA) metabolism to determine the etiology of saturnine gout. His research showed that the enzyme guanase was exquisitely sensitive to lead. Guanase serves to convert the purine guanine to xanthine, which can be converted to uric acid. Guanine is very insoluble, and lead poisoning may lead to accumulation of guanine precipitates in the body. Using the pig as an animal model, a fivefold increase in guanine was observed in extracellular fluid, and crystalline concretions that were identified as guanine were observed in the region of the femoral head. Mercury and silver, but not cadmium or any other metal tested, inhibited guanase activity at low concentrations.

This study has recently been extended to evaluate the effects of lead on purine metabolism in primates since purine metabolism in primates and humans is different than in the lower mammals. Extracellular fluids from lead-poisoned patients will also be examined. Studies will entail the induction of saturnine gout in marmosets and administration of radiolabeled guanine to poisoned and normal animals to determine in which organs guanine accumulates.

The effects of lead and mercury on guanase are synergistic. Research will be undertaken to determine if this synergistic effect is elicited <u>in vivo</u>.

Finally, the tissue distribution of guanase has been studied. The most striking finding was the presence of high guanase activity in the brain of each species tested. Therefore, the possible elicitation of central nervous system (CNS) manifestation by lead and mercury via elevation of nervous tissue guanine will be investigated.

Lead and mercury are volatile components of coal; lead is also an atmospheric contaminant due to its continued use in gasoline. Mercury is a water contaminant. Therefore, this study might indicate the extent to which these pollutants give rise to CNS, renal, and metabolic problems related to the accumulations of the highly insoluble metabolite guanine.

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National Institute on Aging

The National Institute on Aging (NIA) conducts and supports research on projects related to arthritis. Under age 45, the prevalence is greater in men; over age 45, it is equally prevalent in men and women. Several theories about the cause of osteoarthritis have been proposed, but as yet there is not a definite understanding of why and how the disease develops.

NIA researcher Dr. Charles Malemud at Case Western Reserve University in Cleveland has found that cartilage connective tissue macromolecules of osteoarthritic patients differ from those of nonosteoarthritic patients of similar ages. An understanding of these differences is crucial for learning the causes of osteoarthritis. Dr. Malemud has also found evidence that a breakdown of these macromolecules' components after synthesis may play a role in osteoarthritis.

NIA grantees Drs. James Goodwin, Jan Ceuppens, and Martin Rodriquez at the University of New Mexico School of Medicine, Albuquerque, report that nonsteroidal anti-inflammatory agents stimulate cellular immune responses and inhibit production of the rheumatoid factor in patients with rheumatoid arthritis. Nonsteroidal drugs are the initial treatment of choice in patients with rheumatoid arthritis. Previously these agents were thought to have little influence on the course of the disease.

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Division of Research Resources

Rheumatoid arthritis (RA) is being studied extensively at many General Clinical Research Centers (GCRC's). The NIH Division of Research Resources (DRR) supports 75 GCRC's in major U.S. medical centers. Each year, scientists conduct more than 3,000 research studies in GCRC's, with more than 80 percent of the extramural inpatient research funded by NIH taking place in these centers. In addition, extensive outpatient research is also done.

Scientists supported by the Biomedical Research Support (BRS) Program of DRR also are studying RA and other forms of arthritis. This program supports more than 9,000 pilot and regular health-related projects at 546 institutions in the U.S., providing a pool of flexible funds to institutions heavily engaged in Public Health Service-funded research to meet particular needs not normally covered by other grants. The funds may complement or supplement Public Health Service research grants by providing institutions with short-term, emergency, low-cost, interim, and shared resources.

At the GCRC at the Scripps Clinic and Research Foundation in La Jolla, California, Dr. John H. Vaughan and associates have found evidence linking RA and a defective immune response to Epstein-Barr virus, a ubiquitous member of the herpes family. Other researchers have found that RA patients produce an abnormally large number of antibodies to EBV. In addition, previous studies indicate that a hyperactive immune system is responsible for the inflamed joints characteristic of RA. The findings of Dr. Vaughan's team may fill the gap between these two lines of research. The California scientists determined that RA sufferers produce inadequate amounts of interleukin-2, a body chemical necessary for the differentiation of T cells, which produce the virus-fighting protein interferon. Unchallenged by adequate interferon, EBV can proliferate in RA patients and stimulate other agents of the immune system to produce antibodies and enzymes that for unknown reasons attack cartilage and bone.

On the basis of this and other research, Dr. Vaughan speculates that the deficient immune response also may occur with other viruses and lead to RA. Additional studies may point the way to new therapies for RA patients--treatments that rely less on immunosuppressive drugs, which make patients susceptible to secondary infections and cancer, Dr. Vaughan says. He hypothesizes that administering interferon or interleukin-2 to patients could compensate for the immune-system defect and control EBV proliferation, thus reducing the formation of joint-damaging antibodies.

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Many children afflicted with RA also excrete blood in their urine, but the cause of this abnormality, which is called hematuria, has been elusive. In a study of 38 children with juvenile RA at the University of Tennessee GCRC in Memphis, Dr. Bruder F. Stapleton and his colleagues have linked hematuria in young arthritis victims to another urinary disorder--hypercalciuria, or excessive calcium excretion. About 32 percent of the young RA patients studied had elevated calcium levels, compared with 4 percent of the general pediatric population. Half of the patients with the calcium abnormality also suffered from hematuria. On the basis of this study the Tennessee researchers conclude that the calcium abnormality is common among children with RA and that these patients may be at high risk of developing kidney stones. The scientists recommend that children with RA be monitored closely for these complications.

DRR-supported scientists have made other gains against juvenile RA. At the St. Louis University School of Medicine, St. Louis, Missouri, Dr. Terry L. Moore and his colleagues, with the assistance of the University's BRS grant, found abnormal antibodies in 98 of 104 children with juvenile RA. The St. Louis researchers' findings are helping resolve the uncertainties surrounding the cause of this type of RA, which may be complicated by enlargement of the liver, heart disease, and other disorders. Dr. Moore says further research on the role of abnormal antibodies in the development of juvenile RA may improve understanding of this baffling, debilitating disorder, and may allow for early diagnosis of the disease.

An especially severe and rapidly progressive form of arthritis has come under the scrutiny of BRS-supported scientists at the George Washington University (GWU) Medical Center in Washington, D.C. Dr. David G. Borenstein has identified several chemical markers that may assist physicians in early diagnosis of septic arthritis. According to Dr. Borenstein, this disease destroys joint tissues more rapidly than any other form of arthritis, but it often goes undiagnosed when it complicates another inflammatory joint disease, such as gout or RA.

Using the chemical markers they identified in the synovial fluid of patients with septic arthritis, GWU scientists are developing analytical techniques for determining the presence of disease-causing bacteria. Early diagnosis of septic arthritis made possible with such tests would allow for early treatment, saving joints that are in jeopardy of rapid destruction.

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Outlook

Advances in these basic areas of research are enabling investigators to improve methods of diagnosis, develop better ways to surgically correct joints damaged by arthritis, and find new, experimental types of therapy for the many forms of arthritis and related disorders. Ultimately, these findings will lead to the cause and cure of arthritis and a reduction in the devastating impact of these diseases on the Nation's people and its economy.

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